



The Effect of Atenolol on Thyroid Hormons in Subclinical Hyperthyroidism

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Abstract

This Study was performed to evaluate the effect of atenolol on the serum concentration of TT4 and TT3 in subclinical hyperthyroid patients. Due to the insufficient information about the effect of atenolol on serum level of these hormones, the aim of this research was to shade some light on the subject. Fifteen subclinical hyperthyroid patients entered this study. Each patient received 100 mg/day atenolol. The serum concentration of atenolol, TT4 and TT3 were measured before starting the administration of the drug and on the first, third and seventh day after atenolol administration was started. The serum concentrations of TT4, but not TT3, on the third and seventh day were increased significantly in comparison to the baseline TT4. There was no correlation between plasma atenolol concentration and changes in TT4 and TT3.

Keywords: Atenolol; Subclinical hyperthyroidism; TT3; TT4.

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1. Introduction

Beta blockers are effective and useful adjunct drugs in the management of thyroid storm. They are also useful in the management of thyrotoxicosis during pregnancy [1]. All

beta blockers without intrinsic sympathomimetic activity (ISA), such as atenolol, metoprolol and propranolol, are effective in alleviating the hyperthyroid symptoms, but propranolol is the only beta blocker that is reported to inhibit peripheral conversion of T4 to T3 [2]. Treatment of euthyroid and hyperthyroid individuals with propranolol decreases serum T3 concentration [3, 4].

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Moreover it has been reported that the serum concentration of T4 in euthyroid patients has been increased by propranolol [5, 6], however, this level remains unchanged or has slightly increased in hyperthyroid patients [7, 8]. Also in one study the plasma level of propranolol was significantly correlated with decrease in serum concentration of T3 [9]. Atenolol improves the signs and symptoms of hyperthyroidism [10], but there are few studies about the effect of atenolol on the serum concentration of thyroid hormones. In a one week study, there was no significant change in serum T3 concentration in hyperthyroid patients who received 100 mg/day of atenolol, but the serum concentration of T4 showed a small fall [11]. In another study, the administration of atenolol (100 mg/day) for one week lowered T3 but not T4 serum concentration in hyperthyroid patients [12].

There is no study about the effect of atenolol on TT4 and TT3 in subclinical hyperthyroidism. Also there is no study about correlation between concentration of atenolol and serum T4 or T3 in literature. Therefore, this investigation was designed to evaluate: 1) the effect of atenolol on serum TT4 and TT3 in subclinical hyperthyroid patients at different time points after the administration of atenolol, and 2) correlation between the concentration

of atenolol and changes in TT4 and TT3 serum concentrations.

2. Materials and methods

2.1. Materials

Atenolol tablets (100 mg) were provided by Daru-Pakhsh pharmaceutical Co. (Tehran, Iran). Atenolol working standard powder was kindly donated by Sobhan Pharmaceutical Co. (Tehran, Iran). TT4 and TT3 kits were purchased from Iran Kavoushyar Co. (Tehran, Iran). HPLC grade acetonitrile and methanol, and analytical grade sodium dihydrogen phosphate and zinc sulphate were used throughout the study.

2.2. Selection of patients

Fifteen adult subclinical hyperthyroid patients participated in this study. The diagnosis was confirmed by suppressed TSH (TSH <0.5 mIU/l) and normal level of T4 (4.5-12.5 mg/dl) and T3 (80-200 ng/dl). After complete explanation of the aim of the study, all patients signed their informed written consent. Patients with the following parameters were excluded: Younger than 18 and older than 50 years of age; pulse rate under 60/min; systolic blood pressure under 90 mmHg; history of asthma or other bronchospastic disease; pregnant or

Table 1. Demographic data of the patients included in the study.

Case	Age (year)	Weight (kg)	Sex
1	25	56	M
2	19	55	F
3	26	68	F
4	56	67	M
5	25	60	M
6	24	55	F
7	48	70	F
8	19	60	M
9	37	72	F
10	35	70	F
11	41	77	F
12	27	60	M
13	36	81	M
14	22	50	F
15	47	82	F

M: Male; F: Female

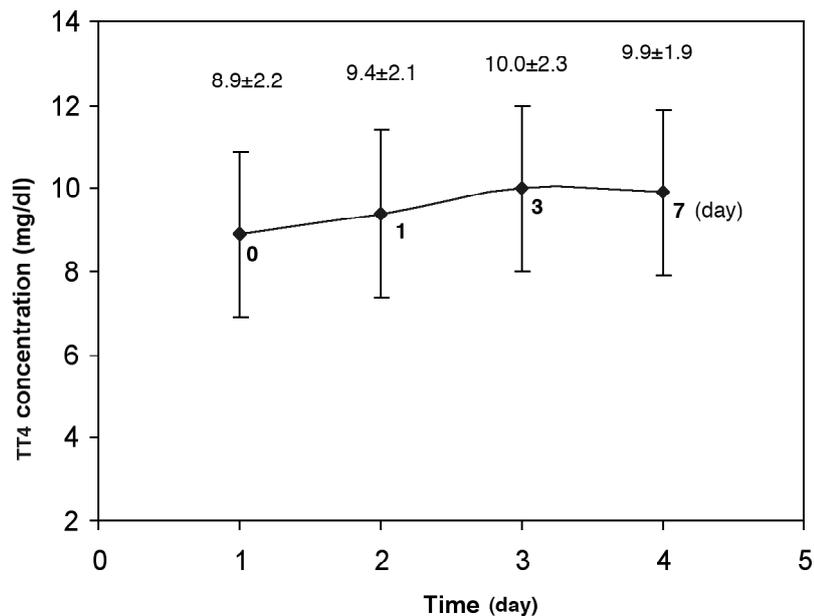


Figure 1. Effect of atenolol on TT4 concentration. TT4 concentration was measured before the administration of atenolol and 3 hours after the administration of atenolol at days one, three and seven after the start of treatment (1: baseline; 2: first day; 3: third day; 4: seventh day).

breastfeeding women; and those who used any drug. Patient's demographic data are shown in Table 1.

2.3. Human study

The protocol of the study was approved by the ethical committee of Tehran University of Medical Sciences. Patients were given 100 mg atenolol per day. Before the administration of atenolol, one blood sample was obtained from each patients to determine baseline TT4 and TT3 and TSH levels. Then three more blood samples were obtained three hours after the administration of atenolol on the first, third and seventh days of the study. Venous blood samples (10 ml) were obtained from forearm vein and collected in heparinized blood tubes. Blood samples were then centrifuged at the room temperature for 15 minutes at 3000 rpm, and plasma was separated and frozen at -70°C until the assay time. Blood pressure and pulse rate of the patients were checked on the days of blood sampling.

2.4. Determination of thyroid hormones

The serum concentration of TT4 and TT3 was determined by radioimmunoassay method with a commercial kit (Iran Kavoushyar). Also, the serum concentration of TSH was determined by IRMA method with the same commercial kit. Reference ranges were: T4 (4.5-12.5 mg/dl), T3 (80-200 ng/dl) and TSH (0.5-5 mIU/l).

2.5. Determination of atenolol concentration

Analysis of the serum level of atenolol was preformed by using an HPLC apparatus from Knauer (Knauer, Germany). The samples were introduced to a Tracer Excel 120 ODS column ($5\ \mu\text{m} \times 150 \times 4.6\ \text{mm}$; Teknokroma, Barcelona, Spain) through an injector fitted by a 50 μl loop. Acetonitril: Phosphate buffer (4:96, pH=6.5) was used as the mobile phase at a flow rate of 1 ml/min. Standard curve of peak area versus analyte concentrations was linear ($r=0.988$) from 50 to 500 ng/ml of atenolol. The intra- and inter-day coefficients of variation were 3.48% and

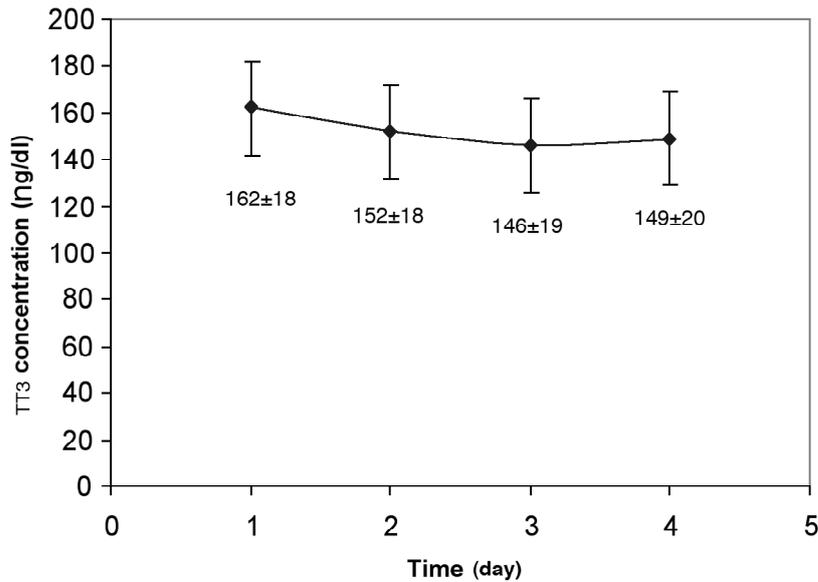


Figure 2. Effect of atenolol on TT3 concentration. TT4 concentration was measured before the administration of atenolol and 3 hours after the administration of atenolol at days one, three and seven after the start of treatment (1: baseline; 2: first day; 3: third day; 4: seventh day).

2.5%, respectively, and the extraction efficiency was 30%.

2.6. Calculations

TT4 and TT3 of the patients, determined before the first dose and three hours after dosing at the first, third and seventh days of study, were called TT4(0), TT4(1), TT4(2), TT4(3) and TT3 (0), TT3 (1), TT3 (2) and TT3 (3), respectively. The difference between the baseline TT4 [TT4 (0)] and each measured TT4 [TT4(1), TT4(2), TT4(3)] were calculated and named as DT4.

$DT4(1) = TT4(1) - TT4(0)$; $DT4(2) = TT4(2) - TT4(0)$; $DT4(3) = TT4(3) - TT4(0)$.

Similar calculations were performed on TT3 and corresponding values were called DT3(1), DT3(2) and DT3(3), respectively. We used SPSS 2000 software for analyzing of our data.

3. Results

TT4 and TT3 serum concentrations were determined in four separate sampling times. Serum T4 showed a small but significant

increase after the third day of administration of atenolol [T4(2)] compared to its baseline level ($p < 0.018$). The serum T4 also showed an increase after the seventh day of atenolol administration [TT4(3) versus baseline T4(0); $p < 0.001$]. Unlike T4, there were no significant differences between baseline T3 [T3(0)] and each of the other measured T3 values [T3(1), T3(2), T3(3)].

Figures 1 and 2 show serum concentrations of TT4 and TT3 at different sampling times. The difference between TT4 and TT3 at sampling time after the drug administration (DT4 and DT3) and their corresponding values at baseline [TT4(0) and TT3(0)] were determined.

Concentrations of atenolol were measured 3 h after atenolol usage on days first, third and seventh of the study and were named as C1, C2 and C3, respectively. Figure 3 shows concentration of atenolol in the sampling days.

4. Discussion

Several studies note that propranolol causes

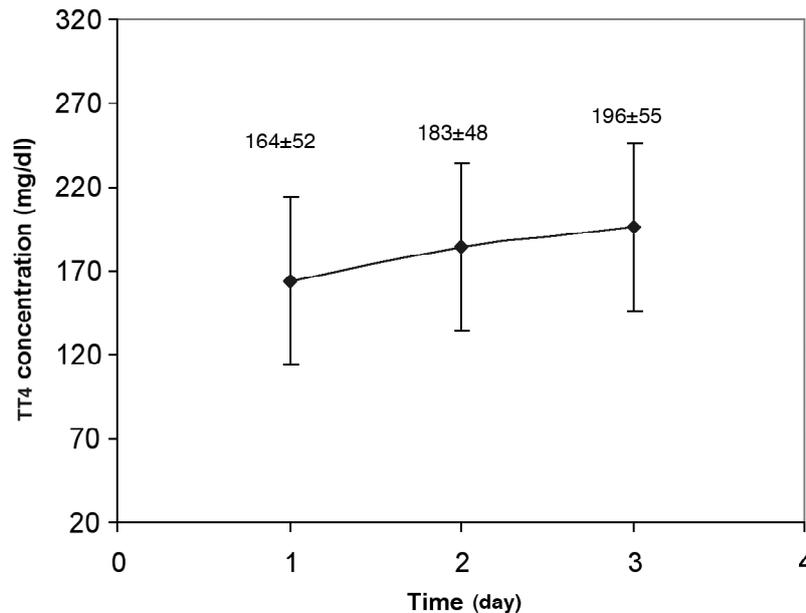


Figure 3. Atenolol serum concentration at different time points measured. The atenolol concentration was measured 3 hours after its administration at days one, three and seven after the start of treatment (1: first day; 2: third day; 3: seventh day).

a significant increase in serum TT4 in euthyroid and hyperthyroid patients [6, 8]. Propranolol has been also shown to decrease TT3 in several studies [3, 4]. The mechanism behind this effect is not known, however, it has been discussed that hepatic concentration of propranolol along with production of its metabolites inhibits T4-5 deiodination which may cause a decline in serum TT3 [13]. Although atenolol and propranolol improve the signs and symptoms of hyperthyroidism [10], several studies have reported different results about the effects of atenolol on serum concentration of TT4 and TT3. In a study which 100 mg/day of atenolol was administered to the subjects, no changes in TT4 and TT3 serum concentration were noted [14]. In another study with the same dose of atenolol, T4 serum concentration was decreased after one week [11]. Lotti *et al.* have reported that the effect of propranolol in decreasing T3 serum concentration could be observed in less than 2 h after the first dose of the drug (i.e. peak time concentration of propranolol) [5]. However, in our study,

atenolol did not change TT3 serum concentration after 3 hours of the first dose (peak time concentration of atenolol). Furthermore, there was no change in serum concentrations of TT4 after 3 hours of the first dose of atenolol. While TT3 was not significantly changed after the third and seventh days of atenolol administration, our study demonstrated that serum concentration of TT4 is significantly increased during the study period. Also, we could not show a significant relationship between serum concentration of atenolol and changes in TT4 [DT4] or TT3 [DT3].

Based on our study in subclinical hyperthyroidism and similar studies in hyperthyroid patients, we suggest that thyroid function tests (especially T4) in these populations may change by atenolol administration.

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